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Report on Carcinogens Draft Substance Profile for Glass Wool Fibers (Respirable) as a Class

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Outline

- Definitions, properties, use, and exposure
- Proposed listing
- Fiber properties and carcinogenicity
- Studies in experimental animals
- Human cancer studies
- Consideration of glass wool fibers as a class

Glass Wool Fibers

- Amorphous fine glass fibers resembling wool; silicon dioxide is the primary chemical component
- Physical properties and chemical composition of different fibers vary; controlled during manufacture
- Fibers break cross-wise
- Commercial fibers are produced as bulk materials that contain a range of fiber dimensions.
- Nominal diameter of fibers
  - Insulation glass wool: 1 to 10 μm (nearly all > 3 μm)
  - Special purpose glass fibers: 0.1 to 3 μm
  - Fiber sizes can overlap, e.g., a 5 μm nominal diameter fiber can have a range of diameters from 1 to 20 μm

Properties of Respirable Fibers

- Respirable fibers can penetrate into the alveolar region of the lung upon inhalation.
- World Health Organization (WHO) fibers (respirable fibers):
  - Aerodynamic diameter < 3 μm diameter > 5 μm length
  - Aspect ratio of at least 3:1 (length/diameter)
- U.S. EPA (respirable)
  - Aerodynamic diameter < 5 μm (humans); < 3 μm (rodents)
  - Aerodynamic diameter takes into account the fiber density and aspect ratio (fiber length/diameter)

Use

- Insulation purposes
  - Weatherproofing, thermal, and acoustical insulation
  - Largest use is for building insulation
  - Produced by rotary centrifugation
- Filtration media – special purpose fibers (SPF)
  - Aircraft and aerospace insulation, battery separators, and high efficiency filters
  - Largest market is for battery separator media
  - Produced by flame attenuation, now also rotary centrifugation

Significant U.S. Exposure

- Exposure: inhalation, ingestion, dermal, ocular
  - Occupational: manufacturing, installation/removal
  - Environmental: indoor air
- Production:
  - 3,388 million pounds of fiberglass were used in commercial and residential building insulation in 2000.
  - 6,000 million pounds of all glass fiber types were produced in the United States in 2002. Approximately 1% are special purpose fibers.

Proposed Listing for Glass Wool Fibers (Respirable) as a Class

Reasonably anticipated to be a human carcinogen

- Sufficient evidence from studies in experimental animals for fibers as a "class"
- Supporting mechanistic evidence

… however, not all glass fibers in the class are carcinogenic

- The dividing line between carcinogenic fibers and non-carcinogenic fibers is not clear

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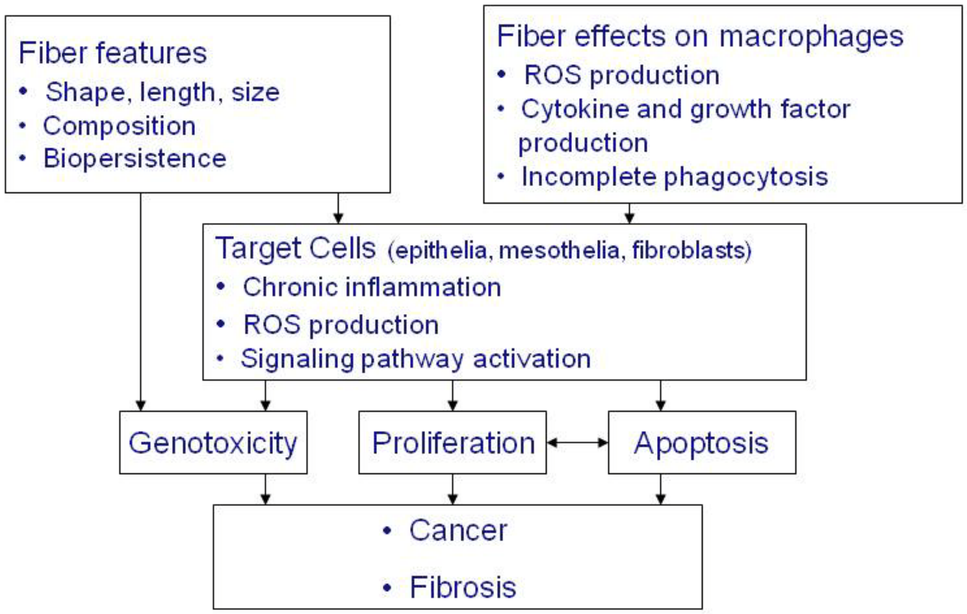
Fibers Properties that Influence Carcinogenicity

- Dose
  - Tumor incidence increases with increasing dose (i.p.) and lesion severity increases with cumulative fiber burden (inhalation).
- Dimension
  - Tumor incidence correlates with fiber size and shape (i.p., i.t.) and longer, thinner fibers are more carcinogenic.
- Durability and biopersistence of fibers in general:
  - K_{dis}, *in vitro* dissolution rate - ng/cm^2/hr
    - Mathematical model that dissolution factor is inversely related to tumorigenicity in i.p. and inhalation study (Eastes and Hadley 1996)
  - $WT_{1/2}$, *in vivo* weighted half-life in days (intratracheal or inhalation)
    - Biopersistence ($WT_{1/2}$) predicts fibrosis in inhalation and i.tr. studies, and tumor response in i.p. studies (Bernstein 2007)

i.p. = intraperitoneal injection
i.t. = intrathoracic placement
i.tr. = intratracheal instillation

Mechanisms of Fiber-Induced Toxicity and Carcinogenicity



ROS = reactive oxygen species

Glass Wool Fibers Are Genotoxic

- *In vitro* positive for:
  - Production of reactive oxygen species (ROS) in cell-free systems
  - Oxidative damage in cultured cells
  - DNA damage to mammalian cells
    - Increase micronuclei, chromosomal aberrations, DNA-DNA interstrand cross links,
    - Proto-oncogene amplification (*K-ras, H-ras, p53, c-fos, c-myc*) and mutations in *K-ras* and *p53* in mouse fibroblasts
- *In vivo* positive for:
  - Strand breaks in rat alveolar macrophages and lung epithelial cells; oxidative stress in rats (i.tr., insulation wool)

i.tr. = intratracheal instillation

Fiber Size Affects Genotoxicity & Cytotoxicity

- Longer fibers are more cytotoxic and genotoxic in mammalian cells.
- Studies in Syrian hamster embryo cultures: longer and thinner fibers have a higher transformation efficiency and cytotoxicity than shorter and thicker fibers.
- Glass wool fibers produced cytotoxicity (measured by relative cloning efficiency) and anchorage-independent growth in mouse fibroblasts.
  - Cell transformation is inversely related to size (length/diameter); the shortest, thinnest fibers are more potent.

Experimental Animal Studies: Route of Exposure

- Inhalation and intratracheal instillation
  - Biologically relevant to human exposure
  - Physiological clearance and properties of fiber
  - Intratracheal instillation by-passes upper respiratory airway and is given as a bolus injection.
- Intrapleural, intraperitoneal, intrathoracic implantation
  - Physicochemical properties of fiber
  - Informative for cancer hazard evaluation
    - Tumor incidence is related to fiber physicochemical characteristics.
    - Hazard ranking of fibers by intraperitoneal injection is similar to that observed by inhalation (Bernstein 2007).

Sufficient Evidence in Experimental Animals for Fibers as a "Class"

- Tumors in multiple species
  - Rats (R)
  - Hamsters (H)
- Tumors by multiple routes
  - Inhalation: lung tumors (R), MCL (R), mesothelioma (R & H)
  - Intratracheal instillation: lung tumors (R & H), mesothelioma (H)
  - Intrathoracic implantation: mesothelioma (R)
  - Intrapleural and intraperitoneal injection: mesothelioma (R)

MCL = mononuclear cell leukemia

Strengths of the Animal Data

- Range of carcinogenic responses observed across fiber types
  - Some experimental fibers (M) were not carcinogenic by i.p.
- Carcinogenic response is stronger for special purpose fibers (SPFs) than for insulation fibers.
  - Mesotheliomas were observed with insulation glass wool after i.p. injection and MCLs after inhalation exposure.
- Data is strongest for the specific SPFs: E glass and 475 glass.

Fiber type	Inhalation	Intratracheal	Intraperitoneal
E glass	Lung tumors, mesothelioma (R)		Mesothelioma (R)
475 glass	MCL* (R)	Lung tumors (R & H)	Mesothelioma, sarcoma (R)
	Mesothelioma (H, MMVF33)	Mesothelioma (H)	Mesothelioma (R, intrapleural)

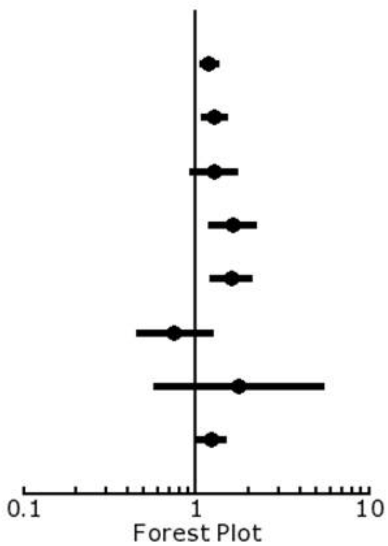
* Mononuclear cell leukemia (MCL)
- Fibers in macrophage aggregates in lung and lymph nodes, increased incidence of MCL
- Combined incidence (M+F) of MCL significant with respect to control group (concurrent and historical)

i.p. = intraperitoneal injection
MCL = mononuclear cell leukemia

Inadequate Evidence of Carcinogenicity in Humans

- Small excess of lung cancer was found across studies of glass wool manufacturing workers
- Magnitude of risk estimates were small enough to be potentially explained by co-exposure to tobacco smoking
- No clear positive exposure-response relationships
- Risk estimates for glass wool are for the "class"
  - Some of the glass wool manufacturing plants included in the U.S. cohort also manufactured special application fibers

Small Excess of Lung Cancer Mortality or Incidence



Study	Analyses[a]	Cases/deaths
U.S.	SMR	243
Europe	SMR	140
Europe	SIR	40
Canada	SMR	42
Canada	SIR	50
France	SIR	5
Russia	Case-control (OR)	10
4 cohorts	Meta-analysis	920[b]

[a] not adjusted for smoking except for Russian study
[b] includes filament workers and glass wool workers from U.S. study

Internal and Exposure-Response Analyses of Lung Cancer in the U.S. Cohort (Marsh & Colleagues)

- Nested case-control study of lung cancer among male glass wool manufacturing workers
  - RR = 1.06 (95% CI = 0.7 to 1.6); 183 cases, smoking adjusted
  - No association with cumulative exposure, average exposure, or duration of exposure to respirable glass fibers
- Female glass wool workers
  - Analyses using glass filament workers as a reference
  - RR = 3.24 (95% CI = 1.27 to 8.28); 6 cases
  - Risks increased with increasing employment duration and latency
  - No association with cumulative exposure
  - Women were exposed to lower levels than men

Other Cancer Sites

- Cancer of the upper respiratory systems and alimentary tract (oral cavity, pharynx, and larynx)
  - Excess risk of cancer incidence was found in European and French cohort studies, not reported in Canadian study
  - Risk increased with exposure duration (French) and latency (European)
  - Meta-analysis (U.S., French, European data)
    - RR = 1.42, 95% CI = 0.9 to 2.1 (head and neck cancer not including larynx)
- Mesothelioma
  - Data inadequate to evaluate

Why are we considering glass wool fibers as a class?

- Individual fibers of the class vary in physicochemical properties.
- Only a subset of fibers has been tested for carcinogenicity.
- Commercial bulk material can contain potentially carcinogenic fibers.

How can we differentiate between carcinogenic and non-carcinogenic fibers and accurately predict the carcinogenicity of untested fibers?

- Studies have demonstrated that dose, dimension, durability, and biopersistence are key factors in determining carcinogenicity.
- Different review groups have agreed that not all fibers are carcinogenic, and divided fibers into separate hazard categories based on parameters related to biopersistence/durability.
  - However, these parameters vary across the review groups.

Parameter: Commercial Application

- In general, SPFs are more durable fibers than insulation fibers, so commercial application is a “surrogate” for biodurability.
- International Agency for Research on Cancer (IARC)
  - Insulation glass fibers: not classifiable as to its carcinogenicity to humans (Group 3)
  - Special purpose fibers (SPFs): possibly carcinogenic to humans (Group 2B)
- Concerns
  - Some overlap in the physicochemical characteristics
    - Size, chemical composition, and Z score (index of solubility)
  - Products with the same use may have different compositions
  - Time-dependent
    - Technology and use can change.
    - Some SPFs being developed today are as soluble or more soluble than some older-type insulation fibers.

Parameter: *In Vitro* Dissolution and Size

- A mathematical model demonstrated that K_{dis} can be related to tumor formation and fibrosis.
  - Fibers with K_{dis} > 100 are unlikely to cause fibrosis after inhalation exposure (Estes and Hadley 1996).
- RoC Expert Panel recommended that special fibers of concern be listed as reasonably anticipated to be a human carcinogen.
  - Fibers ≥ 15 µm length with a K_{dis} ≤ 100 ng/cm^2/h
- Concerns
  - K_{dis} is an important component of biopersistence, but other factors may also be important.
  - Assay is not standardized and laboratories report somewhat different values for the same fibers.
  - Unclear whether the most relevant assay is at pH 7.4 or pH 4.5
  - To date, K_{dis} has not been adopted by regulatory agencies in United States, European Union, or Germany.

Parameter: Weighted Half-Life ($WT_{1/2}$)

- Weighted half-life tests were modeled from biopersistence and collagen deposition (fibrosis) results observed after 2-year inhalation exposure in rats (Bernstein 2007).
- Short-term biopersistence studies can be used to predict average collagen score.
  - $WT_{1/2} \geq 10$ days (inhalation)
  - $WT_{1/2} \geq 40$ days (intratracheal instillation)
- Weighted half-life tests are used by the European Union and Germany in fiber exoneration criteria.

Classification Criteria for European Union (EU) and Germany

- EU and Germany classify all synthetic vitreous fibers (as a class) as possibly or probably carcinogenic.
  - Individuals fibers can be exonerated on a case-by-case basis.
- European Union
  - Fiber with ≤ 6 µm is carcinogenic if solubility index > 18%.
  - Exonerate fiber if pass one of 4 tests.
- Germany
  - Exonerate fiber if it passes one of 3 tests.
  - Fiber with a very high solubility (carcinogenicity index, KI > 40) is exonerated.

Exoneration Criteria (*in vivo* tests)

	EU	Germany
Cancer Bioassay		
IP Injection Test	Negative	Negative
Inhalation Test	Negative	Not used
Biopersistence: Weighted $T_{½}$ life ($WT_{½}$)		
Intratracheal Instillation	$WT_{½}$ < 40 d. > 20 µm length	$WT_{½}$ < 40 d. > 5 µm length
Inhalation	$WT_{½}$ < 10 d. > 20 µm length	Not used

Parameters to Classify Fibers: An Example

Using different parameters to assess biopersistence or durability, different conclusions about carcinogenicity can be reached about two similar insulation fibers (respirable fraction).

- MMVF 10: diameter, 1.13 ± 1.77μm (GMD ± S.D.); K.I.=26.57; Z=28.38
- MMVF 11: diameter, 0.76 ± 1.92 μm (GMD ± S.D.); K.I.=23.97; Z=27.13

	MMVF 10	MMVF 11
Commercial Application	Insulation	Insulation
	Not carcinogenic	Not carcinogenic
K_{dis}* ($ng/cm^2/h$)	300	100
	Not carcinogenic	Carcinogenic
$WT_{1/2}$* by *in vivo* inhalation (days)	14.5 days	9 days
	Carcinogenic	Not carcinogenic

* values from Hesterberg and Hart 2001; K.I.=carcinogenicity index; Z=Z-score; GMD ± S.D.=geometric mean diameter ± standard deviation

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- The dividing line between carcinogenic fibers and non-carcinogenic fibers is not clear.
- Range of carcinogenicity observed
- Fiber properties influence carcinogenicity
- Fibers need to be tested *in vivo* on a case-by-case basis
  - Carcinogenic hazard for commercial materials can only be determined by empirically based testing on a case-by-case basis.
  - Consistent with hazard classification approach of regulatory bodies within the European Union and Germany